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Research Review: The neurobiology and genetics of maltreatment and adversity

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The neurobiological mechanisms by which childhood maltreatment heightens vulnerability to psychopathology remain poorly understood. It is likely that a complex interaction between environmental experiences (including poor caregiving) and an individual's genetic make-up influence neurobiological development across infancy and childhood, which in turn sets the stage for a child's psychological and emotional development. This review provides a concise synopsis of those studies investigating the neurobiological and genetic factors associated with childhood maltreatment and adversity. We first provide an overview of the neuroendocrine findings, drawing from animal and human studies. These studies indicate an association between early adversity and atypical development of the hypothalamic-pituitary-adrenal (HPA) axis stress response, which can predispose to psychiatric vulnerability in adulthood. We then review the neuroimaging findings of structural and functional brain differences in children and adults who have experienced childhood maltreatment. These studies offer evidence of several structural differences associated with early stress, most notably in the corpus callosum in children and the hippocampus in adults; functional studies have reported atypical activation of several brain regions, including decreased activity of the prefrontal cortex. Next we consider studies that suggest that the effect of environmental adversity may be conditional on an individual's genotype. We also briefly consider the possible role that epigenetic mechanisms might play in mediating the impact of early adversity. Finally we consider several ways in which the neurobiological and genetic research may be relevant to clinical practice and intervention. **Keywords:** Child abuse, maltreatment, neuroscience, genetics, HPA, psychopathology, resilience, cortisol.

There is a burgeoning interest in understanding how early adverse experiences impact on the developing brain (e.g., Caspi & Moffitt, 2006; Lupien, McEwen, Gunnar, & Heim, 2009; Teicher et al., 2003). Many clinicians have an intuitive expectation that a more robust neurobiological model of early adversity will not only help us better understand the emergence of developmental psychopathology, but also generate new and innovative approaches to intervention. While there are reasonable grounds to have confidence about the former expectation, there remains a considerable gap between much of our basic neuroscience research and applied clinical practice. Given that the translational work required to bridge these fields is in its infancy, we suggest that at the current time caution is warranted before drawing inferences that directly shape clinical practice. Nevertheless, advances in neuroscience and genetics are rapidly changing how we view early adversity, creating a neuro-biologically informed developmental narrative that has the potential to change social policy, societal perceptions of harm and the conceptual framework within which we think about clinical intervention and prevention.

This paper selectively reviews the recent animal and human research related to early stress, maltreatment and their relationship to psychopathology; a number of earlier seminal studies are also included where these help set the research context. We begin by providing a brief description of what we know about the functioning of biological stress systems, and then review animal, child and adult studies that have investigated how these systems are impacted by adversity. The second and third sections review the evidence for changes at the level of regional brain structure and function respectively. We then consider the evidence from genetic studies, including investigations of gene × environment interactions (G×E) and epigenetic effects, relating these to possible mechanisms associated with vulnerability and resilience. Finally we consider how these basic science findings may (or may not) inform our models of intervention and prevention.

Stress systems and early adversity

1. An overview of key biological stress systems

The body's stress response activates several interlocking biological systems designed to prepare an individual for events that may threaten their well-being or survival. The autonomic nervous system (ANS) provides a rapid response through both sympathetic and parasympathetic systems. Sympathetic activation refers to the classic 'fight-or-flight' response (Cannon, 1929) where increased levels of circulating adrenaline and noradrenaline stimulate heart rate, peripheral vasoconstriction (diverting

blood flow from less essential organs) and energy mobilisation. The reflex parasympathetic system, concerned with the conservation and restoration of energy, can be thought of as the 'brake' which ensures that the excitation of the ANS is relatively short lived. By contrast the hypothalamus–pituitary–adrenal (HPA) axis – one of the core stress response systems – is slower and provides a more protracted response. Stressor exposure triggers corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) release from the paraventricular nucleus of the hypothalamus. These bind to receptors at the anterior pituitary, stimulating secretion of adreno-cortico-trophic hormone (ACTH) which acts on the adrenal cortex to synthesise and release glucocorti-coid hormones (including cortisol in primates and corticosterone in rats). In humans, cortisol promotes the mobilisation of stored glucose and lipid stores and contributes to multiple physiological changes (see Sapolsky, Uno, Rebert, & Finch, 1990 for a review). These effects are adaptive because they prepare an individual to meet the energy demands associated with a stressful event, including vigilance to threat and preparedness to deploy defensive responses. Feedback loops are present at a number of levels in order to modulate responsiveness of the HPA axis and return the system to homeostasis since chronically elevated cortisol levels can have delete-rious effects on health (Lupien et al., 1998; Sapolsky, Romero, & Munck, 2000). The glucocorticoid nega-tive feedback loop is mediated by glucocorticoid receptors (GR) and mineralocoticoid receptors (MR) in several brain regions, notably the hippocampus (Sapolsky et al., 2000). This feedback loop and oth-ers form part of a hierarchical set of control mecha-nisms summating input in order to regulate HPA activity, including those from higher-order forebrain inputs such as the prefrontal cortex and amygdala (Herman et al., 2003). This regulation should pro-duce adaptive responses to social and psychological stressors, preparing the organism to anticipate and respond optimally to threat but returning efficiently to a homeostatic balance when the organism is no longer challenged.

It should be noted that there are several other neuroendocrine, immune system and metabolic pathways engaged in the body's response to stress. CRH in particular plays a key role in mediating mammalian autonomic and behavioural responses, acting as a neurotransmitter. CRH is distributed in a range of brain areas, including the amygdala, hippocampus and cerebral cortex (Swanson, Saw-chenko, Rivier, & Vale, 1983) functioning to coordi-nate behavioural, autonomic and immune responses to stress (Arborelius, Owens, Plotsky, & Nemeroff, 1999). Studies of rats have reported that prolonged early maternal separation reduces the density of CRH binding sites in a number of central regions (Anisman, Zaharia, Meaney, & Merali, 1998), including the amygdala, hypothalamus and hippo-campus where it also mediates loss of branches and spines following stress (Fenoglio, Brunson, & Baram, 2006). The CRH neurons of the central nucleus of the amygdala (CeA), for example, respond positively to glucocorticoids to activate the locus coeruleus, an important site in initiating the catecholamine response (Valentino, Curtis, Page, Pavcovich, & Flo-rin-Lechner, 1998). Indeed, it is thought that the CeA in interaction with several frontal regions (medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC)) plays an important role in mediating an individual's response to expectations of reward and threat based on both past and current experience (Gunnar et al., 2006).

2. The impact of early rearing environment: The HPA axis in rodent and primate studies

Rodent studies that have manipulated mother–pup interactions have demonstrated long-term effects of such manipulations on HPA functioning. Brief peri-ods of handling during infancy (up to 15 minutes per day) serve to stimulate development in so far as these animals become adults showing fewer behavioural indications of anxiety and a more efficient HPA response to environmental stressors (Levine, 1957; Meaney et al., 1996). These effects appear to be partly mediated by an increase in GR expression in the hippocampus (Meaney et al., 1996) and occur alongside other neurobiological changes, including greater amplitude of long-term potentiation in the hippocampus (Wilson, Willner, Kurz, & Nadel, 1986). However, repeated or longer periods of maternal separation show deleterious effects, notably exag-gerated or attenuated HPA axis activity (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Sán-chez, Ladd, & Plotsky, 2001). Increased glucocorti-coid response to subsequent stressors, increased plasma levels of ACTH, fewer GR in the hippocampus and changes in CRF mRNA expression are some of the documented changes observed in HPA function-ing (Anisman et al., 1998; Levine, Wiener, & Coe, 1993; Makino, Smith, & Gold, 1995). These findings indicate that significant disruption to maternal care in the early stages of life is associated with altered HPA axis functioning. Both the timing and the duration of separation are important factors, with more adverse consequences typically associated with earlier and more prolonged separation (De Kloet & Oitzl, 2003). Alongside these neurobiological chan-ges, increases in anxiety-like behaviours, hypervigi-lance and mild cognitive impairments have been reported (Meaney & Szyf, 2005; Sánchez et al., 2001). Importantly, the quality of the maternal behaviour encountered on reunion has been shown to be one factor that can moderate the pup's expe-rience of stress (Liu et al., 1997). Greater levels of maternal licking and grooming behaviour are asso-ciated with a lower HPA response to stress in adult-hood; furthermore, such maternal behaviours

inversely correlate with pup fearfulness and degree of cognitive impairment (Francis, Champagne, & Meaney, 2000). In other words, high levels of licking and grooming are associated with pups that are 'stress resilient'. These findings from studies of rodents demonstrate a profound influence of maternal interaction and separation in the development and regulation of the pup's current and adult HPA system response to stress.

Studies of non-human primates have also investigated the impact of early stress exposure. Human and rhesus monkey infants demonstrate remarkable similarities on separation from their mother (Bayart, Hayashi, Faull, Barchas, & Levine, 1990; Harlow & Suomi, 1971). Chronic and sustained separation leads to a series of significant behavioural and cognitive impairments, including increased fearfulness and anxiety (see Seay & Gottfried, 1975 for a review). However, the impact on HPA functioning in primates is less well understood; one hypothesis is that the initial cortisol response to stress alters the development of dopamine neurotransmission in the prefrontal cortex (Sánchez et al., 2001). More recent studies have deployed subtle manipulations of maternal care; in one study the stress experienced by the mother was artificially increased by making the availability of food when foraging more unpredictable. The foraging demands placed on the mother reduce the amount of time she has to respond to the needs of her infant monkeys. Even 12 weeks of being mothered in such a context is associated with heightened concentrations of cerebrospinal fluid CRF, reduced cortisol levels and fearful behaviours compared to predictably reared control infants (Coplan et al., 1996). When followed into young adulthood, concentrations of CRF remain elevated, indicating that even relatively brief disturbances of the maternal–infant relationship can establish long-lasting changes in stress response systems in monkeys (Coplan et al., 2001). This animal analogue to parenting under conditions of stress provides convincing evidence of a direct effect of environmental adversity on maternal care.

3. The impact of early rearing environment: human studies

Children who have experienced maltreatment. Findings from studies investigating HPA axis activity in children and adolescents with a history of maltreatment are mixed (see Tarullo & Gunnar, 2006 for an excellent review). De Bellis and colleagues reported a blunted ACTH response to CRH challenge but no differences in cortisol response in girls who had been sexually abused (De Bellis et al., 1994). HPA axis response to CRH stimulus has also been investigated by Kaufman and colleagues (1997) who reported ACTH hyper-responsiveness but only among a subsample of maltreated children who were depressed and still exposed to a stressful home environment; no differences were found in cortisol measures (Kaufman et al., 1997). These findings suggest that hyper-responsivity may be contingent on the presence of an ongoing threatening environment. By contrast, Hart and colleagues (Hart, Gunnar, & Cicchetti, 1995) in a study of preschoolers who had experienced maltreatment reported a pattern of cortisol suppression in situations of stress.

Most studies have collected basal cortisol level data given the ethical and practical implications of pharmacological challenge tests with children. Several studies have reported elevated basal cortisol levels (Carrion et al., 2002; Cicchetti & Rogosch, 2001; De Bellis, Baum et al., 1999) while others have reported no differences (Hart et al., 1995). One explanation for these apparently contradictory findings is that elevation is associated with the presence of a concurrent affective disorder (Tarullo & Gunnar, 2006). For example, two studies have reported a rise in cortisol levels across the day for maltreated children with depression but no effects in maltreated children without depression (Hart, Gunnar, & Cicchetti, 1996; Kaufman, 1991). This pattern is also consistent with the elevated ACTH response to CRH in the maltreated-depressed group noted above (Kaufman et al., 1997). Other studies have reported similar elevations in relation to maltreated children with PTSD (Carrion et al., 2002) and dysthymic girls who had been sexually abused (De Bellis et al., 1994). While this pattern of elevated cortisol also characterises non-maltreated children with affective disorders (e.g., Goodyer, Herbert, & Altham, 1998), it is not clear if maltreatment contributes an additional effect (Cicchetti & Rogosch, 2001; Cicchetti, Rogosch, & Cox Kearns, 2001). It should also be noted that several studies of children with antisocial behaviour have reported reduced basal cortisol concentrations and lower cortisol levels when exposed to stress (e.g., McBurnett, Lahey, Rathouz, & Loeber, 2000; van Goozen et al., 1998; see van Goozen & Fairchild, 2008 for a comprehensive review). One possibility is that exposure to early adversity in these children is associated with stress habituation over time, a pattern that may be linked to their difficulties in emotional and behavioural regulation; equally, reduced stress responsivity may emerge as a result of genetic factors, or gene–environment interactions (van Goozen & Fairchild, 2008). A recent meta-analysis has suggested that patterns of diurnal and morning cortisol levels may vary depending on type of antisocial behaviour, patterns of internalising comorbidity, and early environmental adversity (Hawes, Brennan, & Dadds, 2009).

In instances when parenting is compromised but where there is no maltreatment – for example, in the context of maternal depression – there appears to be a link with atypical HPA activity. Halligan and colleagues found that morning salivary cortisol in

adolescents who had been exposed to maternal postnatal depression was elevated and more variable compared to non-exposed peers, a pattern associated with an increased risk of depression (Halligan, Herbert, Goodyer, & Murray, 2004). This finding is consistent with the animal research reviewed above, indicating a link between early adversity (in the form of compromised maternal care) and later risk for psychopathology and atypical HPA functioning.

Adults who have experienced maltreatment as children. In a comprehensive synthesis of over a decade of research Heim and colleagues coherently summarise the evidence for the neural mechanisms mediating childhood maltreatment and adult depression (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). They propose that childhood maltreatment increases the risk of developing depression due to the sensitisation of the neurobiological systems implicated in stress adaptation and response. In an early study using the standardised Treir Social Stress Test (requiring public speaking and mental arithmetic) they reported that women with a history of maltreatment with and without depression exhibited an increased ACTH response compared with controls (Heim et al., 2002). A history of childhood abuse was indeed the strongest predictor of ACTH responsiveness, which in turn was found to be amplified further by trauma in adulthood (Heim et al., 2002). Recently, Heim and colleagues (Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008) used the combined pharmacological test of HPA functioning (the dexamethasone/CRF challenge) with a sample of men with and without childhood maltreatment and current depression. They reported a pattern of increased cortisol response in the context of a failure of the glucocorticoid-mediated negative feedback loop to adequately control HPA activation. These studies suggest that major depression subsequent to childhood maltreatment is associated with inadequate inhibitory feedback regulation of the HPA axis.

A parallel set of research studies has investigated PTSD in a wide range of populations, including those with a prior history of maltreatment. Findings from this literature have been mixed at best (Shea et al., 2004); however, a recent systematic review and meta-analysis supports the view that PTSD is associated with a general pattern of hypocortisolism, with reduced cortisol levels, at least in the afternoon (Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007; see also Yehuda, Golier, & Kaufman, 2005). Furthermore, Meewisse and colleagues (2007) highlight the relationship between lower cortisol levels and PTSD in the context of physical and sexual forms of abuse. These findings therefore indicate a possible dissociation, with HPA hypoactivity in those with maltreatment-related PTSD (Yehuda et al., 2005), but hyperactivity of the HPA system in maltreated individuals presenting with depression (e.g. Heim

et al., 2002). Both may reflect adaptations of the HPA axis in response to different forms of maltreatment and perhaps different periods of onset and chronicity. The inconsistencies across these studies may reflect a range of possible confounds, including the frequently observed comorbidity of depression and PTSD (Newport, Heim, Bonsall, Miller, & Nemeroff, 2004) and, as will be discussed later, the contribution of genetic polymorphisms.

HPA axis development and resilience. There has been a growing interest in understanding the neurobiological basis of resilience (Charney, 2004) and how this might fit within a multiple levels of analysis framework for understanding maltreatment and psychopathology (Curtis & Cicchetti, 2003; Cicchetti & Rogosch, 2007). Several recent studies have now investigated the neurobiological features present in individuals with a prior history of maltreatment with *no* evident psychopathology; such work is of direct relevance to understanding possible neurobiological correlates of resilience (Carpenter et al., 2007, 2009; Elzinga et al., 2008; Gonzalez, Jenkins, Steiner, & Fleming, 2009; Heim et al., 2009; Klaassens et al., 2009; Tyrka et al., 2008). These studies have tended to report patterns of hypocortisolism, consistent with the notion of a hypothesised trajectory of initial hyperactivation of the HPA system progressing (after an adaptive process of down-regulation) to a state of chronic adrenal stress hyporeactivity (Carpenter et al., 2009). Whether this hypocortisolism reflects a risk factor for future psychiatric disorder or a correlate of resilient functioning in these individuals is currently unclear.

Summary: Stress systems and early adversity

A substantial evidence base from the animal literature delineates long-term effects on HPA system functioning following disruption to adequate maternal care; these effects persist into adulthood and are accompanied by stable behavioural changes (Meaney & Szyf, 2005). The accumulating evidence that early trauma, including physical, sexual and emotional abuse, is associated with increased risk of psychopathology in adulthood including depression, post-traumatic stress disorder (PTSD), alcohol and substance abuse and borderline personality disorder (Bebbington et al., 2009; Beitchman et al., 1992; Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Draijer & Langeland, 1999; Kendler, Kessler, Neale, Heath, & Eaves, 1993; McCauley et al., 1997; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Stein et al., 1996). In view of the persuasive evidence from the human and animal literature of the link between stress and HPA functioning there is a strong case that early stress may lead to an ongoing dysregulation of the HPA axis which in turn predisposes to psychiatric vulnerability in later life (van Goozen & Fairchild, 2006, 2008). While there is

consensus around this general principle, the putative mechanisms of how the HPA axis might mediate the link between stress and psychopathology and the precise nature of any interaction remain less clear (see Miller, Chen, & Zhou, 2007 for a helpful meta-analysis).

Structural brain differences associated with maltreatment

The previous section focused predominantly on research linking early stress with HPA axis functioning and development. However, an equally important strand of research relates to how stress influences neural structure and function. For example, animal studies have shown that disruption to maternal care in rats is associated with lower levels of neurotrophins which support neural plasticity, an effect particularly evident in the PFC (Roceri et al., 2004). Such findings are consistent with the observed deficits in attention observed in maternally deprived pups (e.g., Lovic & Fleming, 2004) and the attentional and executive functioning deficits observed in maltreated children (e.g., Beers & De Bellis, 2002). We consider studies that have investigated differences in brain structure followed by the limited findings that relate to the possible impact of maltreatment on brain function.

1. Hippocampus

Children who have experienced maltreatment. A substantial body of animal research has shown that the hippocampus plays a central role in learning and various aspects of memory (Mizomuri, Smith, & Puryear, 2007) and that these functions are impaired in animals that have been exposed to chronic stress (McEwen, 1999). De Bellis, Keshavan et al. (1999) were the first to report that maltreated children with PTSD presented with smaller intracranial and cerebral volumes, smaller corpus callosum and larger lateral ventricular volume compared to healthy, non-maltreated children. It was notable that the expected decrease in hippocampal volume, based on previous studies of adults with PTSD, was not observed. Since that time, over ten sMRI studies of children and adolescents with PTSD following maltreatment have consistently failed to detect the adult pattern of lower hippocampal volume (e.g., Carrion et al., 2001; Jackowski, De Araújo, De Lacerda, De Jesus Mari, & Kaufman, 2009; Mehta et al., 2009; Woon & Hedges, 2008).

Adults who have experienced maltreatment as children. By contrast, with the exception of one study (Pederson et al., 2004), reduced volume of the hippocampus has generally been reported for adults who have experienced maltreatment as children (Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006; Vythilingam et al., 2002; see Woon & Hedges, 2008 for a review). Two explanations have been proposed to account for the discrepancy of child and adult findings (see Lupien et al., 2009). The *neurotoxicity hypothesis*, based on data from both animal and human studies, postulates that stress-induced prolonged exposure to glucocorticoids can lead to a reduction in hippocampal cell complexity and even cell death (Gould & Tanapat, 1999; Sapolsky et al., 1990; Uno, Tarara, Else, Suleman, & Sapolsky, 1989; Watanabe, Gould, & McEwen, 1992). In humans, therefore, hippocampal volume reduction may result from years or decades of PTSD or chronic stress. In support of this hypothesis, Carrion and colleagues (2007) reported that cortisol levels and PTSD symptoms at baseline predicted the degree of hippocampal volume reduction over an ensuing 12- to 18-month interval in 15 maltreated children with PTSD (Carrion, Weems, & Reiss, 2007). Alternatively, the *vulnerability hypothesis* posits that a smaller hippocampal volume in individuals with maltreatment-related PTSD is not a consequence of stress, but rather a predisposing risk factor for PTSD present in some individuals prior to any traumatic experience (Gilbertson et al., 2002). Longitudinal studies or studies taking advantage of identical twins discordant for maltreatment exposure are required to distinguish these competing accounts.

2. Amygdala

Children who have experienced maltreatment. The amygdala plays a key role in evaluating potentially threatening information, fear conditioning, emotional processing, and memory for emotional events (see Phelps & LeDoux, 2005). Given the importance of each of these processes in environments characterised by threat and unpredictability, it may be expected that differences in amygdala structure would be associated with exposure to childhood maltreatment (Lupien et al., 2009). While one study by Mehta and colleagues (2009) reported an increase in amygdala volumes, especially on the right, in maltreated adolescents compared to their peers (Mehta et al., 2009), a recent meta-analysis of children with maltreatment-related PTSD did not find significant differences in amygdala volume between maltreated and non-maltreated children (Woon & Hedges, 2008).

Adults who have experienced maltreatment as children. To date, only three studies have examined amygdala volume in adults with a history of childhood maltreatment; one found reduced volume in female patients with dissociative identity disorder as compared to healthy females (Vermetten et al., 2006) while the other two reported no measurable differences (Andersen et al., 2008; Bremner et al., 1997). While it is too early to draw definitive conclusions regarding impact of maltreatment on amygdala

development, these preliminary findings suggest that the amygdala may be more resistant to gross structural change relative to other brain structures.

3. Corpus callosum and other white matter tracts

Children who have experienced maltreatment. The corpus callosum (CC) is the largest white matter structure in the brain and controls inter-hemispheric communication of a host of processes, including, but not limited to, arousal, emotion, and higher cognitive abilities (Giedd et al., 1996; Kitterle, 1995). Crucially, in terms of development, nerve fibre connections passing though this region are fully formed before birth, with myelination continuing throughout childhood and adulthood (Giedd et al., 1996; Teicher et al., 2004). Teicher and colleagues (2004) have speculated that different regions of the CC might have different windows of vulnerability to early experience. With the exception of one study (Mehta et al., 2009), decreases in CC volume (particularly middle and posterior regions) have been reported in maltreated children and adolescents compared to non-maltreated peers (De Bellis & Keshavan, 2003; De Bellis, Keshavan et al., 1999; De Bellis et al., 2002; Jackowski et al., 2008; Teicher et al., 2004). Furthermore, preliminary evidence suggests that these effects are characterised by sex-dependent differences (De Bellis & Keshavan, 2003; Teicher et al., 2004).

In a recent DTI study, Eluvathingal and colleagues (2006) found decreased fractional anisotropy values (a measure that assess white matter fibre tract direction and density) in the left uncinate fasciculus (which connects the OFC to the anterior temporal lobe, including the amygdala) in maltreated children compared to controls (Eluvathingal et al., 2006).

Adults who have experienced maltreatment as children. A study of adult females with maltreatment-related PTSD has also reported smaller volume of the CC as compared to healthy controls (Kitayama et al., 2007). More recently, a recent DTI study in a non-clinical sample examined the effects of severe parental verbal abuse (e.g., ridicule, humiliation, and disdain) on brain connectivity; three white matter tracts were reported to show reduced fractional anisotropy (Choi, Jeong, Rohan, Polcari, & Teicher, 2009). The authors hypothesised that these abnormalities may underlie some of the language and emotional regulation difficulties seen in victims of childhood maltreatment (Choi et al., 2009).

4. Prefrontal cortex, cerebellum and visual cortices

Children who have experienced maltreatment. The PFC is extensively interconnected with other cortical and subcortical regions consistent with its major role in the control of many aspects of behaviour, cognition, and emotion regulation (Davidson, Putnam, & Larson, 2000; Fuster, 1997; Miller & Cohen, 2001; Ochsner & Gross, 2005). There are mixed findings from studies comparing PFC volume of children with maltreatment-related PTSD and non-maltreated children. One study reported no group difference (De Bellis, Keshavan et al., 1999), but another found smaller prefrontal volume and prefrontal white matter (De Bellis et al., 2002) in the maltreated group, while the two most recent studies – one using voxel-based morphometry (VBM) – observed larger grey matter volume of the middle-inferior and ventral regions of the PFC in the maltreated groups (Carrion et al., 2009; Richert, Carrion, Karchemskiy, & Reiss, 2006). The reasons for these inconsistent findings are not clear, but differences in age range of participants across studies and the variation in maltreatment/adversity type (i.e., sexual abuse vs. witnessing violence) and exposure (single vs. multiple) may account for some of the discrepancies. Methodological differences across studies might also partly account for the inconsistent findings. Indeed, most of the early sMRI studies of maltreatment included visual inspection of the scans by experienced radiologists and manual tracing methods for calculating regional brain volumes of structures of interest. However, over the past decade, automated techniques such as VBM have been developed which avoid subjective visual assessment and allow the study of the entire brain across large groups of participants (Ashburner & Friston, 2000; Whitwell, 2009). Finally, it is also possible that there are specific windows of vulnerability in brain development or that the effects of adversity may only manifest at a critical point of brain development (even if this occurs substantially after the adversity takes place). For example, some of the youngest children in the existing studies had not yet reached a crucial period of PFC synaptic organisation. Consistent with this hypothesis, Andersen et al. (2008) observed in a cross-sectional study that grey matter volume of the frontal cortex was maximally affected by abuse at ages 14–16 years, while the hippocampus and CC were maximally affected at ages 3–5 years and 9–10 years, respectively.

Finally, decreased cerebellar volume in children and adolescents with a history of maltreatment has been a consistent finding in the literature (Bauer, Hanson, Pierson, Davidson, & Pollak, in press; Carrion et al., 2009; De Bellis & Kuchibhatla, 2006). The cerebellum is best known for its role in the coordination of motor behaviour (Bastian, Mugnaini, & Thach, 1999). However, there is growing evidence that it plays a crucial role in emotion processing and fear conditioning via its connection with limbic structures and the HPA axis (Schutter & van Honk, 2005). The cerebellum has also been shown to be involved in executive functioning (Schmahmann, Weilburg, & Sherman, 2007), which is impaired in children with a history of maltreatment (Beers & De Bellis, 2002).

Adults who have experienced maltreatment as children. In a non-clinical sample, Tomoda, Suzuki et al. (2009) found that harsh childhood corporal punishment was associated with reduced grey matter volume in the left dorsolateral PFC and the right medial PFC. The DLPFC is a necessary structure for aspects of higher cognitive processing, such as working memory, while the medial PFC is central to aspects of social cognition such as self-knowledge, person perception and mentalising (Amodio & Frith, 2006). In another study, in comparison to healthy individuals, patients with major depressive disorder who reported a history of childhood maltreatment exhibited reduced volume of the rostral ACC, which was negatively correlated with both cortisol levels and scores on the Childhood Trauma Questionnaire (Treadway et al., 2009). Despite important limitations (such as the lack of information on the age of onset and duration of maltreatment), this study suggests that the rostral ACC, like the hippocampus, might be vulnerable to prolonged glucocorticoid exposure resulting from chronic stress, which in turn may decrease its ability to exert negative feedback control over HPA activity (Treadway et al., 2009). Finally, in a community sample, Tomoda and colleagues selected females who had been sexually abused, but with no other forms of maltreatment, and compared them to females who had not been abused (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009). Compared with the non-abused females, there was a reduction in grey matter volume in the left and right primary visual cortex of the sexually abused females.

Functional brain differences associated with maltreatment

Children who have experienced maltreatment. In contrast to the number of studies examining structural brain differences, only a few have investigated possible functional correlates associated with maltreatment using imaging techniques such as fMRI, positron emission tomography (PET) or electrophysiological modalities. In the only published fMRI study to date with children, Carrion and colleagues used a Go/No-Go task assessing sustained attention and response inhibition and compared the brain activity of young adolescents with post-traumatic stress symptoms (PTSS) secondary to maltreatment to that of age- and gender-matched healthy controls (Carrion, Garrett, Menon, Weems, & Reiss, 2008). The adolescents with PTSS showed relatively decreased activation of the left dorsolateral PFC, but increased activation in the mPFC and ACC. Chugani and colleagues used PET in the awake resting state to investigate the brain activation associated with early global deprivation in pre-adolescent children adopted from Romanian orphanages where the children had experienced adverse early rearing

environments (Chugani et al., 2001). Compared to adult and child control groups, the adopted children showed decreased metabolism in a network of areas implicated in stress regulation, including the OFC.

While the main strength of fMRI and PET are their good spatial resolution in relation to brain activity, event-related potentials (ERP) record the brain's electrical activity and yield detailed information about the temporal sequence (resolution in milliseconds) of cognitive operations throughout the brain (i.e., mental chronometry). Much of the existing ERP research has compared the pattern of brain response of adversely treated children and healthy children when processing facial expressions, an ability that is usually mastered by the preschool years (Izard & Harris, 1995). When compared with never institutionalised children, institutionalised children who have experienced severe social deprivation show a pattern of cortical hypoactivation when viewing emotional facial expressions (Parker & Nelson, 2005), and familiar and unfamiliar faces (Parker et al., 2005). A second set of important studies by Pollak and colleagues has revealed that school-aged children who had been exposed to physical abuse and neglect allocate more attention to angry faces (Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak, Klorman, Thatcher, & Cicchetti, 2001) and require more attentional resources to disengage from such stimuli (Pollak & Tolley-Schell, 2003). Similar findings have recently been obtained with toddlers who experienced maltreatment in their first year of life (Cicchetti & Curtis, 2005). These ERP findings suggest that some maltreated children allocate more resources and remain hyper-vigilant to potential social threat in their environment, possibly at the expense of other developmental processes.

Adults who have experienced maltreatment as children. Dillon and colleagues have recently investigated reward processing in adults with a history of childhood maltreatment, using fMRI (Dillon et al., 2009). Using a monetary incentive delay task they found that these adults, relative to peers with no history of adversity, rated reward-predicting cues as less positive, exhibiting a blunted brain response to reward cues in the left pallidus. This result suggests a possible link between childhood adversity and later depressive psychopathology.

A number of PET studies of adults have now been conducted; all but one (Bremner et al., 2005) have compared women survivors of childhood sexual abuse with and without PTSD (Bremner et al., 1999; Bremner et al., 2003; Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004). Unfortunately, the absence of a group of non-abused women without PTSD means that these studies could examine only the effects of PTSD and not the effects that might be related specifically to childhood abuse. These studies have relied on a variety of tasks, including script-driven imagery to prompt specific

memories of a traumatic event (Bremner et al., 1999; Shin et al., 1999), paragraph encoding to examine verbal declarative memory (Bremner et al., 2003), fear conditioning to assess basic emotional processing (Bremner et al., 2005), and the emotional Stroop paradigm to investigate the influence of emotion on attention (Bremner, Vermetten et al., 2004). For example, Bremner and colleagues compared women with abuse-related PTSD to non-abused, healthy women on a fear-conditioning paradigm (Bremner et al., 2005). They reported increased amygdala activation during fear acquisition and reduced ACC activation during extinction in the clinical group. However, it is not clear if the group differences were due to PTSD or to the experience of the abuse.

Summary: structural and functional brain differences associated with maltreatment

There is relatively consistent evidence for reduced corpus callosum and cerebellar volume in individuals who have experienced adversity and no differences in relation to the hippocampus. The structural findings are more mixed for the PFC. In terms of functional findings, extant studies suggest that experience of maltreatment is associated with hypoactivity in several brain regions, including certain regions of the PFC and the limbic and paralimbic systems; ERP studies have found that children who have experienced severe social deprivation show a pattern of cortical hypoactivation that resembles the findings of the PET study by Chugani and colleagues (Chugani et al., 2001). Atypical responses to angry faces in prefrontal regions have also been observed, indicating increased attentional monitoring for social threat.

The genetics of resilience and vulnerability

Do genetic differences account for individual differences in resilience and vulnerability?

Many recent studies have measured the biological impact of environmental adversity by taking into account genetic differences that may constrain the stress response and increase the likelihood of resilience versus vulnerability following maltreatment (Moffitt, Caspi, & Rutter, 2005). Twin and adoption studies have demonstrated that many of the psychiatric outcomes that are associated with maltreatment, such as PTSD, depression and antisocial behaviour, are partly heritable (e.g., Koenen, Nugent, & Amstadter, 2008; Rhee & Waldman, 2002; Sullivan, Neale, & Kendler, 2000). In other words, individual differences in susceptibility to these disorders are partly driven by genetic influences. Despite demonstrable heritable influences, it would be erroneous to claim that there are genes for PTSD, depression or antisocial behaviour. Instead there are

genetic variants each adding a small increment to the probability that someone may develop or be protected from developing a psychiatric disorder (Plomin, Owen, & McGuffin, 1994). It is thought that these genetic variants act across the lifespan by biasing the functioning of several brain and hormonal circuits, which are crucial for effecting a stress response (Viding, Williamson, & Hariri, 2006).

For example, linkage and association studies have implicated variants within several genes, such as monoamine oxidase-A (MAOA), brain-derived neurotrophic factor (BDNF), serotonin transporter (5-HTT), and cathecol-o-methyl transferase (COMT) in the aetiology of PTSD, depression and antisocial behaviour (e.g., Craig, 2007; Feder, Nestler, & Charney, 2009). Several issues should be borne in mind when considering these genetic findings. Firstly, for every study reporting a positive association between a gene and a disorder there seem to be an equal or larger number of negative findings. This is not surprising. Given the assumed small main effect of any single gene on behavioural outcome, the reliable detection of a main effect will require a degree of statistical power that is beyond most existing studies. Secondly, although the genes influencing stress reactivity are likely to act in an additive manner, gene–gene interactions have also been reported to drive individual differences in stress reactivity; for example, carrying two risk-associated gene variants may confer a greater level of vulnerability to stress reactivity compared to the combined risk conferred by each separately (e.g., Jabbi et al., 2007; Kaufman et al., 2006). Thirdly, several gene environment interaction (G×E) studies have demonstrated that in addition to conferring vulnerability to environmental adversity, genetic make-up can also denote resilience. Finally, the vulnerability effects exerted by the genes do not appear to be disorder specific. In other words, the same risk genes are often implicated in the aetiology of several disorders associated with maltreatment/adversity. For example, 5-HTT has been associated with PTSD, depression and antisocial behaviour (e.g., Cicchetti, Rogosch, & Sturge-Apple, 2007; Feder et al., 2009).

The interaction of genes and environment in conferring risk or resilience

There is intuitive appeal of a biologically driven predisposition (genes) interacting with environmental factors to produce an individual's phenotype (i.e., the classic notion put forward by the stress-diathesis model). G×E research has taken off in recent years following the first seminal reports of gene–environment interaction by Caspi, Moffitt, and colleagues (Caspi et al., 2002; Caspi et al., 2003). Much of this work has focused on outcomes of early stress and maltreatment as a function of genotype. Caspi et al. (2002) were the first to report on an interaction of a measured genotype (MAOA) and environment

(maltreatment) for a psychiatric outcome and demonstrated that individuals who are carriers for the low-activity allele (MAOA-l) are at an increased risk for antisocial behaviour disorders following maltreatment. This finding has since been replicated by several other research groups (see Taylor & Kim-Cohen, 2007; Weder et al., 2009) and imaging genetic studies have found that the risk, MAOA-l, genotype is related to hyper-responsivity of the brain's threat detection and reduced activation in emotion regulation circuits, as well as to structural differences (in males) in key regulatory regions, such as OFC (Buckholtz et al., 2008; Eisenberger, Way, Taylor, Welch, & Lieberman, 2007; Meyer-Lindenberg et al., 2006). This work suggests that a mechanism by which MAOA genotype engenders vulnerability to (reactive) aggression following maltreatment may include increased and poorly regulated neural reactivity to threat cues in the environment (Viding & Frith, 2006).

G×E studies have also focused on the role of HPA axis genes in moderating risk following childhood abuse. For example, Binder et al. (2008) found that polymorphisms in FKBP5, a gene that has been shown to regulate glucocorticoid receptor sensitivity, moderated the likelihood of developing PTSD following childhood abuse. This G×E interaction was paralleled by FKBP5 genotype-dependent and PTSD-dependent effects on glucocorticoid receptor (GR) sensitivity, as measured by dexamethasone suppression test, suggesting a mechanism by which the genotype effects may moderate vulnerability to PTSD following childhood abuse. Alterations in FKBP5 functioning may be involved in abnormal GR-mediated signalling in neurons that are involved with stress response.

Both example studies summarised above suggest that genotypes potentially serve as predictors of both risk and resilience for adult psychiatric outcomes for people who have survived childhood maltreatment and abuse. G×E research has also suggested that positive environmental influences, such as social support, can ameliorate genetic and environmental risk for psychopathology and promote resiliency. Kaufman and colleagues demonstrated that children with genetic vulnerability (BDNF Met allele and two 5-HTT short alleles) and environmental risk (maltreatment) were less likely to develop depression if they had social support (Kaufman et al., 2006). This finding illustrates the important point that when considering a G×E interaction, positive environmental influences (such as contact with a supportive attachment figure) are as relevant to consider as negative environmental influences.

Epigenetics and the impact of early rearing environment

The risk effects of a gene may never manifest if that gene is not actually expressed. The regulation of gene expression has been proposed as a potential molecular mechanism that can mediate maladaptations (vulnerability) as well as adaptations (resilience) in the brain (Tsankova, Renthal, Kumar, & Nestler, 2007). These 'epigenetic' mechanisms refer to complex processes which regulate gene activity without altering the underlying DNA sequence. As outlined earlier, animal research has established the link between variations in maternal behaviour (such as licking, grooming and arched-back nursing) and the development of an animal's HPA axis response to stress. We now know that epigenetic regulation is a candidate mechanism through which caregiving behaviours may produce long-lasting effects on HPA activity and neuronal function (e.g., Weaver et al., 2004). In other words, epigenetic modification of gene expression may help explain the link between a set of maternal behaviours (high licking and grooming early in life) and more modest HPA responses to stress (Weaver et al., 2004); this link is likely to be mediated at the level of hippocampal GR expression and GC feedback sensitivity. One striking finding from this work is that cross-fostering reversed the epigenetic methylation changes associated with less attentive maternal care, highlighting the ongoing importance of environmental influences (both positive and negative) in shaping the stress response at the biological level. Such reversibility has important implications for intervention.

To date, there remains a paucity of animal studies investigating epigenetic effects of maltreatment per se. One exception is a recent study by Roth and colleagues who employed a rodent model in which infant rats were exposed to stressed caretakers that showed abusive behaviours (Roth, Lubin, Funk, & Sweatt, 2009). They reported that early maltreatment produced persisting changes in methylation of BDNF DNA. Critically, the methylation changes altered BDNF gene expression in the adult prefrontal cortex. This finding is extremely interesting as it documents 'epigenetic' effects of maltreatment in brain areas that are known to be both structurally and functionally altered in humans following maltreatment. Roth et al. (2009) also observed altered BDNF DNA methylation in the *offspring* of these females that had previously been exposed to maltreatment as pups. This suggests the possibility of a trans-generational transmission of changes in gene expression and behaviour associated with early maltreatment, even in a new generation of animals that had not been exposed to such environmental stressors.

We know of only one human epigenetic study that has assessed the effects of maltreatment on gene expression. McGowan and colleagues observed differences in epigenetic regulation of hippocampal glucocorticoid receptor expression (including increased cytosine methylation of an NR3C1 promoter) in suicide victims with a history of childhood abuse, as compared with either suicide victims with

no childhood abuse or controls (McGowan et al., 2009). Interestingly, the epigenetic effects observed in the childhood abuse victims of this human study were comparable to the effects observed for the rats with low licking and grooming and reduced arched-back nursing mothers (Weaver et al., 2004). To our knowledge, no studies have looked at how baseline genotype differences may limit the extent and nature of epigenetic changes to provide a more mechanistic understanding of G×E.

Summary: genetics of resilience and vulnerability

There are genetic influences on individual differences in the psychiatric outcomes associated with maltreatment. Recent G×E studies suggest that certain polymorphisms may confer vulnerability or resilience to maltreatment, for example in terms of later levels of PTSD, depression, or antisocial behaviour. Epigenetics is providing an exciting new avenue of research that aims to understand the mechanisms by which gene expression is influenced by exposure to environmental stressors and protective factors.

Limitations of current research

It is important to highlight several limitations that characterise many of the research studies investigating maltreatment. Firstly, researchers in the field have struggled to recruit and assess samples of children and adults that are readily comparable. Samples labelled 'maltreated' have often been highly heterogeneous, drawn from different contexts (e.g., residential settings vs. home environments) and characterised by very different maltreatment histories. There is an increasing recognition of the need to improve the construct validity of measures that assess maltreatment type (Herrenkohl & Herrenkohl, 2009) as well as improve our accuracy in gauging maltreatment severity (Litrownik et al., 2005). Future studies need to meet the challenge of becoming more systematic in delineating maltreatment type, chronicity, frequency and even perpetrator identity in their samples if findings across studies are to be meaningfully compared. There are some notable exceptions where researchers are already working to address these challenges (e.g. Andersen et al., 2008; Cicchetti & Rogosch, 2001). Secondly, as noted earlier, many studies of adults and children have tended to recruit individuals with PTSD, particularly studies assessing structural brain differences. This approach makes it difficult to tease apart effects unique to maltreatment experience and current psychopathology. Thirdly, there remains a remarkable dearth of fMRI studies of children; at the current time, most fMRI studies pertaining to maltreatment have been of adults who retrospectively reported childhood experiences of abuse. Finally, it is worth noting the relatively small sample sizes that have characterised some of the studies reviewed here, particularly several neuroimaging studies. There are undoubtedly real practical barriers that make recruiting such samples of children difficult, but larger samples would certainly add confidence to the findings as well as allow us to better understand individual differences. These limitations should act to caution any strong conclusions regarding the neurobiological developmental trajectories of children experiencing maltreatment. The hypothesis that childhood maltreatment leads to dysregulation of the HPA axis and aberrant brain development, thereby increasing psychiatric vulnerability, remains precisely that – an hypothesis; further work, including longitudinal studies, is required to strengthen this case.

Clinical implications

This review has outlined an array of neurobiological effects associated with early adverse rearing environments. Such effects can, on the one hand, be viewed as a cascade of deleterious changes in brain structure and function that are harmful for the developing infant. However, a more evolutionary and developmentally informed view would suggest that such changes are in fact adaptive responses to an early environment characterised by threat. If the infant is to respond optimally to the challenges posed by their surroundings then early stress-induced changes in neurobiological systems can be seen as 'programming' or calibrating the stress system to match the demands of a hostile environment; this will in turn maximise an individual's ability to compete for resources and survive to sexual maturity (Liu et al., 1997; Teicher et al., 2003; Lupien et al., 2009). Two core assumptions make such atypical adaptation of clinical relevance. The first is that chronic exposure to early stress establishes a neurobiological response associated with a higher biological cost and increased risk of mental and physical health problems (e.g., Arborelius, Owens, Plotsky, & Nemeroff, 1999; Dallman et al., 2004; McEwen, 1999). The second is that this pattern of neurobiological adaptation shapes how emotional and cognitive systems mediate social interaction (Pollak et al., 2001; Pollak, Vardi, Bechner, & Curtin, 2005). Early established patterns of hypervigilance or under-arousal can become maladaptive in normative environments, e.g., when the child is at school, increasing vulnerability for behavioural, emotional and social difficulties.

In our view, neurobiological and genetic research has genuine potential to inform clinical practice (see the Special Issue of *Development and Psychopathology*, including Cicchetti and Gunnar (2008), for an excellent overview). We wish to highlight three examples. Firstly, this research can provide an

integrated developmental narrative of how disruption to early caregiving can impact on a child's psychological and emotional development. Maternal behaviour, for example, is predictive of how well very young infants respond to everyday stressors: infants with mothers demonstrating higher-quality maternal behaviour, including greater sensitivity, show lower cortisol responses (Albers, Marianne Riksen-Walraven, Sweep, & Weerth, 2008). Such variation in normative samples illustrates how sensitively the neurobiological system is calibrated by the behaviour of the caregiver who is tasked both with creating a safe micro-environment for the child and with helping them regulate their own emotional states. In other words, patterns of sensitive, responsive and attentive caregiving provide an external mechanism to regulate glucocorticoid and other stress responses (Gunnar & Donzella, 2002; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). This 'scaffolding' for the child's stress regulation provided by the caregiver appears to be particularly important during childhood when the HPA system may go through a quiescent stage – a stress hyporesponsive period (SHRP) – that protects the developing brain (Gunnar & Cheatham, 2003; Levine, 1994). The animal and human studies reviewed above illustrate the consequences of maltreatment where such scaffolding is markedly absent. Here children are forced to regulate their own levels of stress; indeed, the caregivers themselves may be the source of stress for the children. As we have seen, this may lead to developmental adaptation of the HPA axis, with psychological and biological consequences that increase long-term vulnerability for psychopathology (Gunnar & Cheatham, 2003). Therefore our goal as professionals is to understand how to create better structures around children – essentially a systemic scaffolding – to help them more effectively regulate stress so that it does not derail normative neuro-cognitive development. We suggest that such a developmental narrative, informed by neuroscience, will increasingly shape our clinical formulation and in particular our understanding of how we can minimise developmental risk and promote resilience.

Secondly, we would highlight the future potential of neurobiological and genetic research to identify biomarkers that may help to predict treatment outcome more effectively. In clinical practice we are routinely asked to assess children for therapeutic intervention and make decisions as to what form of therapy would be more effective (for example, CBT versus psychoanalytic child psychotherapy). Although such interventions are costly and time consuming, even our best efforts as clinicians often fail to elicit improvement. It does not help that our clinical model for accurately predicting 'what works best for whom' is largely informed by diagnostic criteria based on behavioural features. We may find that genetic and neurobiological biomarkers do not fit tidily with existing diagnostic frameworks and, as our knowledge increases, we may need to revise our diagnostic systems. Furthermore, identification of such biomarkers may shed light on psychological mechanisms of change. For example, do changes reflect a normalisation of brain response or are they associated with the instantiation of compensatory patterns of activity? While a number of adult imaging studies have demonstrated the potential for levels of functional brain activation in specific brain regions to predict treatment response to CBT (Schienle, Schäfer, Stark, & Vaitl, 2009), this approach is quite impractical in routine clinical practice. However, it does raise the possibility that neuropsychological screening informed by biomarker research or perhaps ERP approaches may one day help us better predict differential treatment outcome. Similarly, genotype markers may also help predict differential treatment responsiveness. For example, it has been demonstrated that response to a parenting intervention for externalising problems in infants depends on which form of the dopamine receptor (D4) gene the child is carrying (Bakermans-Kranenburg, Van IJzendoorn, Mesman, Alink, & Juffer, 2008). There will, of course, be ethical implications that will need careful consideration in relation to such innovations (van Goozen & Fairchild, 2008).

Thirdly, there is the possibility that we may be able to use neurobiological markers (perhaps, one day, even measures of epigenetic change) to index treatment response; this may be particularly pertinent for very young children unable to provide accurate self-report. Pioneering work in this field includes that of Mary Dozier (Dozier, Manni et al., 2006; Dozier, Peloso et al., 2006) and Phil Fisher at the Oregon Social Learning Center (Fisher & Stoolmiller, 2008; Fisher, Stoolmiller, Gunnar & Burraston, 2007). Dozier and colleagues, for example, looked at the patterns of cortisol change in children following an intervention with foster parents that aims to explicitly improve their ability to regulate the level of stress of the child in their care (Dozier, Manni et al., 2006; Dozier, Peloso et al., 2006). Children whose foster parents received this attachment-based intervention essentially showed a normalisation of cortisol responses to a social stressor (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008), demonstrating that treatment response can be measured at the neurobiological level.

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Key points

- Advances in neurobiological and genetic research are providing us with a more detailed and integrated understanding of the impact of childhood maltreatment.
- Children exposed to such adversity may be vulnerable to developing an atypical HPA response to stress that increases their risk for later psychopathology.
- Neuroimaging evidence points to structural and functional brain differences that may underpin the psychological and behavioural problems associated with childhood maltreatment.
- As research advances, an awareness of such biological influences should increasingly help clinicians understand psychological mechanisms of risk and resilience.
- In future, biological markers may provide novel ways of predicting treatment response and measuring treatment outcome.

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